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Could androgens protect middle-aged women from cardiovascular events? A population-based study of Swedish women: The Women's Health in the Lund Area (WHILA) Study

A. Khatibi, C.-D. Agardh, Y. A. Shakir, C. Nerbrand*, P. Nyberg*, J. Lidfeldt* and G. Samsioe*

Departments of Clinical Sciences in Lund and *Malmö, Lund University, Lund, Sweden

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ABSTRACT

Objective The aim of this analysis was to delineate perceived associations between androgens and cardiovascular events in perimenopausal women.

Design A cross-sectional, population-based study of 6440 perimenopausal women aged 50–59 years, living in Southern Sweden. In all, 461 (7.1%) women were premenopausal (PM), 3328 (51.7%) postmenopausal without hormone therapy (HT) (PM0) and 2651 (41.2%) postmenopausal with HT (PMT). For further comparisons, 104 women (1.6%) who reported cardiovascular disease (CVD) were studied in detail; 49 had had a myocardial infarction, 49 a stroke and six women both events. For each woman with CVD, two matched controls were selected ($n = 208$).

Results In the matched controlled series, androstenedione levels were lower ($p < 0.005$) in cases. Cases with hormone therapy had also lower testosterone levels than matched controls ($p = 0.05$). In the total cohort, by using multiple logistic regression analyses, testosterone was positively associated with low density lipoprotein cholesterol ($p < 0.001$) and high density lipoprotein cholesterol (HDL-C) ($p < 0.001$) in all women, but negatively associated with levels of triglycerides in both the PM0 ($p < 0.001$) and PMT ($p < 0.001$) groups. Androstenedione levels were positively associated with HDL-C ($p < 0.05$) and negatively with triglycerides ($p < 0.05$) in the PM group.

Conclusion Women with cardiovascular disease had lower serum androgen levels, particularly women using hormone replacement therapy, even when controlled for lipids and other potential risk factors.

Correspondence: Dr A. Khatibi, Department of Gynecology and Obstetrics, Lund University Hospital, S-221 85 Lund, Sweden

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INTRODUCTION

Androgens exert important physiological effects in women. They are not only the precursor hormones for estrogen biosynthesis in the ovaries and extragonadal tissues, but appear also to act directly, via androgen receptors, on several body systems. Androgen levels decline with age in women and it is nowadays accepted that many postmenopausal women experience a variety of physical symptoms secondary to androgen depletion, as well as physiological changes that may affect the quality of life[1].

Testosterone is a biologically potent androgen with specific receptors and target tissues. It is secreted into the circulation by both the adrenals and the ovaries. It is also formed within the target tissue from circulating dehydroepiandrosterone sulfate (DHEAS). During the reproductive years, approximately 25% of circulating testosterone originates from the ovaries, about 25% from the adrenal glands and about 50% from peripheral androstenedione conversion. In aging women, circulating testosterone remains stable well into the age of about 80 years. Although ovarian volume decreases by about 30%, the ovarian stroma, driven by high undulating menopausal gonadotropins, secretes testosterone in increasing abundance. Testosterone production thus decreases little after menopause, even if adrenal androgen production of DHEAS and androstenedione declines substantially[2].

Hence, the decline in androstenedione after menopause is greater than that of testosterone. Nonetheless, several years after menopause, levels of androstenedione and testosterone are significantly lower than values in premenopausal women[3].

Sex hormones play a major role in determining the risk of cardiovascular disease (CVD). There is growing evidence on direct associations between normal androgen levels and reduced cardiovascular morbidity and mortality in women[4]. After menopause, the influence of estrogens declines, whereas that of androgens increases[4].

Testosterone and sex hormone binding globulin (SHBG) both decrease after menopause but the decrease in serum SHBG is more pronounced, which is one explanation for increased androgenic manifestations in postmenopausal women, such as increased facial hair and lowered voice[5].

While several studies have shown that reduced serum levels of SHBG were associated with increased serum levels of insulin and triglycerides and decreased high density lipoprotein cholesterol (HDL-C) levels in premenopausal women, little information is available for postmenopausal women[6].

Until now, only few small studies have been directed to determine the effects of androgens on women's lipid profile and cardiovascular system. The aim of this analysis was to delineate perceived associations between androgens and cardiovascular events in perimenopausal women and to highlight associations with cardiovascular risk factors, particularly pertaining to lipid metabolism.

METHODS

This report is an analysis from The Women's Health in the Lund Area (WHILA) Study. The WHILA project covered all women ($n = 10\,766$) born between December 2, 1935, and December 1, 1945, living in the Lund area, Sweden, by December 1, 1995. The Lund area is located in southern Sweden and composed of a university town with $\sim 100\,000$ inhabitants, and its surrounding rural areas, mainly farmland, with a population of $\sim 50\,000$ inhabitants. Women were invited to a screening procedure, which took place between 1996 and 2000. Of the total population of 10 776 women, 6917 (64.2%) completed the generic questionnaire and underwent a physical and laboratory assessment. Of this number, 6440 contributed to the hormonal determination and were included in the present analysis. The main reasons for non-response were: immigrants with poor knowledge of Swedish, moving out of the community prior to appointment offered, refusal, severe disease, or death. The age distributions were similar in the responders and non-responders. More non-responders than responders died during the following 2 years, 1999–2000 (1.5% vs. 0.3%, $p < 0.001$). The main causes of death were cancer and cardiovascular disease (CVD). Of the total population, around 5% were chronically ill or disabled and could not participate; another 10% were immigrants with insufficient knowledge in the Swedish language and therefore did not participate. Hence, participants were representative of ambulant middle-aged Swedish women. A detailed analysis of non-responders has been published elsewhere[7,8]. A population register comprising all inhabitants identified women eligible for the study. Informed consent was obtained and the ethics committee at Lund University approved the study. A specially trained midwife nurse collected the questionnaires at the time of

the examinations and personally interviewed each woman, and potential problems were addressed. At the interview, 19% of the subjects made some corrections in their written answers caused by mistakes or misunderstandings when filling out the forms. The questionnaires were answered before the laboratory results were obtained. The physical examination included measurements of body weight, height, minimal waist and maximal hip circumference (WHR), systolic and diastolic blood pressures, random capillary blood glucose and a lipid profile.

Women were divided into three groups according to their hormonal status: premenopausal (PM), postmenopausal without hormone therapy (PM0) and postmenopausal with hormone replacement therapy (PMT). Menopause was defined as a bleed-free interval of at least 12 months. The women with hormone replacement therapy used mostly combined oral hormone therapy composed of estradiol and norethisterone acetate.

For each woman with CVD ($n = 104$), two controls were selected ($n = 208$) matched for age (± 1 year), smoking habits, body mass index (± 2.0), WHR ($\pm$ 0.19), low density lipoprotein cholesterol (LDL-C) ($\pm$ 0.8 mmol/l), HDL-C (± 1.0 mmol/l), diastolic blood pressure (± 10.0 mmHg) and hormonal status.

Laboratory analysis

Serum levels of triglycerides, total cholesterol, HDL-C and LDL-C were measured by a Cholestech LDX instrument (Cholestech Corporation, Hayward, CA, USA) on capillary whole blood. The instrument measured values within a range for serum cholesterol between 2.59 and 12.90 mmol/l, for serum HDL-C between 0.39 and 2.59 mmol/l, and for serum triglycerides between 0.51 and 7.34 mmol/l. Serum LDL-C was calculated according to Friedewald's formula. For further details about lipids and lipoproteins measurements see reference 8.

ELISA techniques were used for the determination of serum androstenedione, SHBG, cortisol, insulin, and leptin levels using commercial monoclonal antibodies (DRG Instrument GmbH, Marburg, Germany). KRYPTOR®-Testosterone, KRYPTOR®-Estradiol 17β (estradiol) are kits designed for KRYPTOR automated immunofluorescent assays of testosterone and estradiol in human serum (BRAHMS AG, Germany). KRYPTOR® uses TRACE® (Time Resolved Amplified Cryptate Emission) technology, based on a non-radiative transfer of energy. This transfer takes place between two fluorescent tracers. Detection limits and coefficient of variations for hormones were as follow: estradiol, 3.5 pmol/l and 6.0%; testosterone, 0.15 nmol/l and 6.4%; androstenedione, 0.15 nmol/l and 5.14%; SHBG, 4.0 nmol/l and 3.0%, respectively[9].

A testosterone index was defined as testosterone/SHBG $\times$ 100. This index was calculated to consider potential differences between free and protein-bound steroids[10]. The estradiol/testosterone ratio was also calculated for further statistical analysis.

Statistical analysis

For continuous variables, when normally distributed, Student's t test was used for determination of differences between groups. When not normally distributed, the Mann–Whitney test was used. Multiple linear regression analyses, controlling for age, body mass index and smoking habits (method stepwise) were performed to evaluate associations between androgens and serum lipids. p Values < 0.05 were regarded as statistically significant. The Bonferroni correction method was applied when needed for multiple comparisons. Calculations were performed using the statistical program SPSS version 13.0 (SPSS Inc, Chicago, Il, USA).

RESULTS

According to the hormonal status, participating women ($n = 6440$) were divided into three groups, i.e. 461 (7.1%) were premenopausal (PM) with regular menstruation, 3328 (51.7%) postmenopausal without hormone therapy (PM0), and 2651 (41.2%) postmenopausal with hormone therapy (PMT).

A total of 104 (1.6%) reported a history of CVD: 49 had had a myocardial infarction, 49 a stroke and six women had had both, of which 74 (71.2%) were PM0 and 30 (28.8%) were PMT.

When cases with CVD were compared to matched controls, androstenedione levels were lower ($p < 0.005$) for cases. Lower androstenedione ($p < 0.01$) and testosterone ($p = 0.05$) levels were found in the case group but for the PMT women only (Table 1).

In the total series, the three perimenopausal groups were compared by their hormone levels (Table 2). The PMT group had lower testosterone and androstenedione but higher estradiol and SHBG levels when compared to the PM0 group ($p < 0.001$). The PMT group had lower

Table 1 Comparisons of sex hormone levels in case and control groups in all subjects, postmenopausal women without hormone therapy (PM0), and postmenopausal women with use of hormone therapy (PMT). Data are given as median (interquartile range)

	Androstenedione (nmol/l)	*Testosterone* (nmol/l)	*Testosterone index*	*SHBG* (nmol/l)	*Estradiol/testosterone ratio*
All subjects					
Case ($n = 104$)	3.1 (2.1)	1.8 (1.4)	3.2 (5.4)	48.4 (42.2)	144.1 (0.0197)
p Value	0.004	0.15	0.30	0.92	0.61
Control ($n = 208$)	4.0 (3.1)	1.9 (1.6)	3.7 (4.5)	52.0 (35.6)	138.8 (0.0207)
PM0					
Case ($n = 74$)	3.1 (2.3)	1.9 (1.18)	3.7 (5.4)	46.7 (36.6)	76.2 (0.0079)
p Value	0.98	0.62	0.46	0.66	0.61
Control ($n = 148$)	3.7 (3.3)	2.0 (1.6)	4.0 (5.4)	47.0 (36.4)	72.3 (0.0084)
PMT					
Case ($n = 30$)	3.0 (2.1)	1.3 (1.4)	2.3 (5.2)	57.6 (59.3)	62.6 (0.0498)
p Value	0.005	0.05	0.36	0.49	0.62
Control ($n = 60$)	4.3 (2.3)	1.8 (1.7)	2.6 (3.8)	60.4 (30.9)	59.4 (0.0782)

SHBG, sex hormone binding globulin.

Table 2 Comparison of median hormone levels in premenopausal women (PM), postmenopausal women without hormone therapy (PM0), and postmenopausal women with use of hormone therapy (PMT). Data are given as median (interquartile range)

	PM ($n = 461$)	*PM0* ($n = 3328$)	*PMT* ($n = 2651$)	*Differences between groups*	*p Value for the three groups*
Testosterone	2.08	2.09	1.80	β^{**}, δ^{**}	**
Androstenedione	4.17	4.10	3.70	β^{**}, δ^{**}	**
Estradiol	96.32	15.30	85.32	α^{**}, β^{*}, δ^{**}	**
SHBG	57.10	51.92	64.62	α^{**}, β^{**}, δ^{**}	**
Estradiol/testosterone ratio	0.156	0.033	0.165	α^{**}, δ^{**}	**

$^{*}p < 0.05$; $^{**}p < 0.001$.
α, Statistical difference between PM and PM0; β, statistical difference between PM and PMT; δ, statistical difference between PM0 and PMT; Bonferroni corrections for multiple comparisons were performed.

testosterone and androstenedione but higher SHBG levels compared to the PM group ($p < 0.001$). When comparing the PM with the PM0 group, SHBG as well as estradiol levels were higher in the PM group ($p < 0.001$) (Table 2).

By multiple linear regression analyses (Table 3), testosterone was positively associated with total cholesterol, LDL-C and HDL-C, but negatively with triglycerides in both the PM0 and PMT groups. For androstenedione, associations were found only in the PM group, being positive for HDL-C ($p < 0.05$) and negative for triglycerides ($p < 0.05$). SHBG was positively associated with HDL-C ($p < 0.001$) in all groups, but negatively with triglycerides in the PM ($p < 0.01$) and PMT ($p < 0.001$) groups. SHBG was negatively associated with serum LDL-C when assessed in all women but not separately in the groups. Estradiol was negatively associated with total cholesterol and LDL-C in the PM0 ($p < 0.001$) and PMT ($p < 0.001$) groups. There were negative associations between androgens and triglycerides ($p < 0.001$) but positive ($p < 0.001$) for HDL-C. For LDL-C, there was a positive association with testosterone ($p < 0.001$) but negative ones with estradiol ($p < 0.001$) and SHBG ($p < 0.001$). The associations for serum lipids and estradiol/testosterone ratio resembled associations for serum lipids and estradiol (Table 3).

DISCUSSION

The WHILA study is a cross-sectional, population-based study of middle-aged women, containing information about lifestyle, health status, body composition, hormone and lipid

Table 3 Multiple linear regression analyses on serum lipids and hormone levels in different hormone groups. Controlled for age, smoking, body mass index

	Serum lipids (B)†			
Hormones	*Total cholesterol*	*Triglycerides*	*LDL-C*	*HDL-C*
Testosterone (nmol/l)				
All	+0.040*	−0.103***	+0.056***	+0.034***
PM	ns	ns	ns	ns
PM0	+0.029*	−0.152***	+0.031*	+0.041***
PMT	+0.078*	−0.110***	ns	+0.036***
Androstenedione (mmol/l)				
All	ns	ns	ns	ns
PM	ns	−0.131*	ns	+0.068*
PM0	ns	ns	ns	ns
PMT	ns	ns	ns	ns
SHBG (nmol/l)				
All	ns	ns	−0.001***	+0.001***
PM	ns	−0.003**	ns	+0.001**
PM0	ns	ns	ns	+0.001**
PMT	ns	−0.001*	ns	+0.001***
Estradiol (pmol/l)				
All	−0.001***	ns	−0.001***	ns
PM	ns	ns	ns	ns
PM0	−0.001***	ns	−0.001***	ns
PMT	−0.001***	ns	−0.001***	ns
Estradiol/testosterone ratio				
All	−0.230***	ns	−0.203***	ns
PM	ns	ns	ns	ns
PM0	−0.325**	ns	−0.272*	ns
PMT	−0.113*	ns	−0.121**	ns

+, Positively associated; −, negatively associated; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ns, no significant association; †unstandardized coefficients B value.
LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; SHBG, sex hormone binding globulin.

profiles[7,8]. This analysis was one primary objective of the WHILA project, which was designed to study CVD, diabetes and its risk factors in women. In the present matched control–case series, lower levels of serum androgens were shown to be associated with cardiovascular events. To the best of our knowledge, androgen levels have not previously been shown to be linked to cardiovascular events in women. Existing studies mostly discuss androgens and their perceived influence on risk factors of cardiovascular disease, with conflicting conclusions. By studying actual cardiovascular events, this study adds further possibilities to address perceived associations between endogenous androgens and CVD.

A further review of the literature of androgen actions affecting the circulatory system indicated early enthusiasm for use of testosterone in patients with CVD, followed by subsequent disenchantment with androgens due to negative effects on lipid metabolism, and again renewed interest as new technologies and a better understanding of the cardioprotective effects of estrogens have led to re-examination of the beneficial and adverse effects of androgens[11]. Literature data on androgens and cardiovascular risk factors are conflicting, with reports showing both positive and negative effects[12–18].

In our matched control series, androgen levels, and particularly androstenedione levels, were lower in cases compared to controls, indicating a protective effect of androgens. As cases and controls were matched for important cardiovascular risk factors such as age, smoking habits, body mass index, WHR, LDL-C, HDL-C and diastolic blood pressure and also adjusted for hormonal status, it is suggested that androgens exert beneficial effects by additional mechanisms

other than those that relate to these risk factors, as supported by previous studies[18–22].

In the total series, associations were shown for androgens with HDL-C and triglycerides, indicating lower CVD risks. However, no consistent association was found between androgens and LDL-C.

Mudali and colleagues showed that SHBG was positively associated with a more favorable lipid profile, including lower total and LDL-C levels as well as triglycerides and higher HDL-C levels in their control group[12]. In line with our study, Noyan and colleagues also showed a positive correlation between SHBG and HDL-C[11].

Bataille and colleagues found a negative correlation between triglycerides and SHBG as well as total testosterone, but positive correlation between HDL-C and SHBG as well as total testosterone; these resemble our results. They suggested that SHBG might be a central factor in the hormonal regulation of the lipid profile[13]; this could be a plausible explanation for the results.

A clinical trial showed that low plasma SHBG concentrations were associated with increased total body fat and also subcutaneous abdominal and intra-abdominal adipose tissue in premenopausal middle-aged women[14]. Low SHBG levels were also associated with higher triglyceride levels, higher cholesterol/HDL-C ratio, but lower HDL-C concentrations; these are similar to our data.

Furthermore, Haffner and colleagues showed that SHBG was inversely correlated with body mass index and positively with HDL-C and HDL-C/total cholesterol ratio. Total and free testosterones were significantly and inversely correlated with the HDL-C/total cholesterol ratio. Total testosterone concentrations were also positively correlated with total cholesterol, body mass index, and systolic and diastolic blood pressures[15].

In our study, SHBG levels were predominantly in the range 50–65 nmol/l. At this concentration, free androgens are less than 0.5% of the total hormone concentration and the difference in free hormone levels at SHBG concentrations between 50 and 65 nmol/l is negligible[16]. Consequently, we chose not to consider different effects of free and protein-bound androgens.

Desmeules and colleagues suggest that the postulated sensitivity of lipolytic enzymes to androgens and estrogens is reflected by a strong negative association between SHBG levels and hepatic lipase, and a lower-magnitude positive association of this hormonal parameter to lipoprotein lipase activity in women. These associations appear to be independent of a concomitant variation in total adiposity or body fat distribution[17]. The effect of testosterone on serum lipids, with an increase in HDL-C level but a decrease in triglycerides, appears to be a physiologic response. Increased levels of LDL-C, a well-known cardiovascular risk factor, might be due to the stimulation of hepatic lipase or lipoprotein lipase by androgens, which, in turn, causes a rapid elimination of very low density lipoprotein (VLDL) cholesterol particles to LDL-C. Some studies suggest other protective effects than lipoproteins for androgens on CVD[18–22], such as direct effects on the vascular wall and effects mediated by a modified inflammatory response.

Taken together, accumulating data suggest that androgens could be protective for cardiovascular disease in middle-aged women. The mechanisms behind this protection are not fully understood but apparently comprise effects on traditional risk factors such as lipids and lipoproteins, but our data also suggest that additional mechanisms are waiting to be outlined further and these are important. It is suggested that a part of this protective effect is anti-atherogenic via reduction of the atherogenic serum lipid profile. Androgens stimulate hepatic lipase and lipoprotein lipase activity and thereby remove serum triglycerides. This might be of importance, since high triglyceride levels are a pivotal risk factor for CVD in women. One possibility could be that a rapid conversion of triglycerides to VLDL cholesterol, which then transforms to LDL-C particles, causes LDL-C accumulation. These accumulated LDL-C particles are suggested to be of the less atherogenic type and not of the small dense type[23].

From a lipid point of view, a combination of estradiol and testosterone seems favorable. This may have implications for the choice of progestin co-medication in hormone therapy, and a progestin with some androgenic properties could be preferred.

CONCLUSION

Women with cardiovascular disease had lower serum androgens levels, particularly women using hormone replacement therapy, even when controlled for lipids and other potential risk factors such as age, smoking habits, body mass index, waist to hip ratio and diastolic blood pressure. Hence, androgen could be a protective factor for cardiovascular disease and this warrants further studies.

Conflict of interest Nil.

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